Myasthenia Gravis: Brief Guide to Diagnosis and Management

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■ *Physicians should consider the possibility of myasthenia gravis in patients complaining of fluctuating muscle weakness and easy fatigability. The disorder may occur in either sex at any age. Repeated measurements of multiple muscle groups and functions to include baseline strength and response to a control as well as anticholinesterase drugs are desirable in reaching a diagnosis. Appropriate doses of anticholinesterase medication reduce weakness and fatigability in most patients. Selected patients may benefit from thymectomy. Patients in crisis failing to respond to anticholinesterase drugs, having difficulty maintaining a patent airway or adequate respiratory exchange are best managed by prompt tracheostomy using a cuffed tube, with adequate tracheobronchial toilet and mechanical respiratory assistance.*

MYASTHENIA GRAVIS IS a disorder manifested by varying weakness and excessive fatigability of the voluntary muscles of the body. Following a brief period of rest, there is at least a partial recovery of strength.[13] The exact cause of myasthenia gravis is unknown. The possibilities under consideration include a circulating neuromuscular blocking agent similar to curare,[23,24] an autoimmune process in which the body makes antibodies against its own muscle,[20,21] a defect in the production or liberation of acetylcholine at the neuromuscular junction,[2,22] and a slow virus infection with long latency and low virulence.[4] The disorder is not new. Early descriptions are credited to Thomas Willis in 1672.[12] Erb and Goldflam gave more extensive descriptions of myasthenia gravis toward the end of the 19th century. It is sometimes called the Erb-Goldflam disease or myasthenia gravis pseudoparalytica.

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Pathology

There are no specific pathological findings; however, voluntary muscle biopsy may show collections of lymphocytes, called lymphorrhages. Muscle atrophy and necrosis are less frequently seen.[3,17] Studies of the neuromuscular junction by special techniques may show irregular elongation of the motor end-plates as well as preterminal branching.[25] Thymic enlargement with lymphocytic germinal centers is common. Thymomas also are frequent.

Incidence and Forms

The exact incidence of the disorder is unknown since it is not reportable to health authorities. Estimates range between one to 40,000 and one to 10,000 of the general population.[10]

The disorder occurs in both sexes at any age and in any race. It is more common in women in their late teens and before the age of 40 and in men after the age of 40.[16] It is not directly inherited, but there is a greater familial incidence than might be expected by sheer chance.[10] Two forms of the disorder occur in infancy. One is a transient, neonatal myasthenia occurring in some newborns of myasthenic mothers. This seldom lasts more than a few days or weeks, following which the infant is normal. The other form is congenital myasthenia gravis occurring in infants of non-myasthenic mothers. This is a relatively permanent form of the disease. It is often more symmetrical in distribution than the adult form, but similar in other respects.

Symptoms and Signs

Symptoms of the disorder are characteristically fluctuating and evanescent early in its onset. They may consist of varying amounts of any of the following, alone or in various combinations: drooping of one or both eyelids, double vision, facial weakness and difficulty smiling, trouble chewing, trouble swallowing, trouble talking, weakness of the neck, difficulty raising the arms above the head, weakness of the arms, forearms and hands, with difficulty extending the fingers, difficulty flexing the thighs at the hips and weakness in the lower limbs, particularly in attempting to walk on the heels. These symptoms are summarized in Table 1. The weakness and fatigability are often worse in the presence of intercurrent infection, emotional stress, menstrual periods, sleep loss and increased physical activity.

The signs of muscle weakness and fatigability are similarly evanescent early, are variable and are asymmetric in amount and distribution. Some patients have a relatively restricted form of the disease, involving, for example, the extraocular muscles. Others may have a patchy distribution and in others the distribution may be more generalized. Ptosis of the eyelids is usually asymmetric and fluctuating. Upward, medial and lateral movements of the eyes are more frequently limited than downward movement. Again, the involvement of the extraocular muscles is asymmetrical. Pupillary responses are generally normal. The muscles closing the jaw are more frequently involved than those opening it, so that the patient may support his chin with his hand or use his hand to close his jaw in order to chew. Among the facial muscles,

TABLE 1.—*Common Initial Symptoms of Patients with Myasthenia Gravis**

Symptom	Incidence (Per Cent) in Males	Females	All Patients
Drooping eyelids	24	26	25
Double vision	55	31	41
Difficulty talking	7	23	16
Difficulty swallowing and regurgitation	5	14	10
Difficulty chewing	11	5	7
Weakness of hands and fingers	4	10	7
Weakness of legs	9	17	13
General weakness	5	15	11

*Findings from 177 patients with myasthenia gravis (102 females and 75 males) seen by the author in the myasthenia gravis clinic and Division of Neurology at UCLA School of Medicine, Los Angeles.

the orbicularis oculi is often more extensively involved than the orbicularis oris and buccinator. The face is relatively smooth and often expressionless because of weakness. The risorius is frequently spared, the phenomenon resulting in a sneering expression where a smile is intended. Weakness of the muscles of the soft palate and pharynx often accompany dysarthria and dysphagia. The patient may find protruding the tongue into either cheek difficult or impossible.

The neck flexors are more commonly involved than the extensors, and where that imbalance occurs the patient has difficulty raising his head from the supine position. Often the deltoids are involved and the patient has difficulty abducting and extending the arms at the shoulders or raising them above the head. The biceps or the triceps muscles, or both, may be involved, with varying degrees of weakness in flexing and extending the forearms at the elbow. Wrist extensors and, in particular, the finger extensors are more frequently and severely involved than finger flexors. Weakness and fatigability among the intrinsic muscles of the hand are common within the thenar and hypothenar groups, in particular the abductor pollicis brevis and abductor digiti quinti. Weakness of the infraspinati at the shoulders is manifested by difficulty in externally rotating the arms at the shoulders with elbows at the side.

Varying degrees of weakness and fatigability of the respiratory muscles, including intercostals, diaphragm, and accessory muscles of respiration, may be manifest by shallow breathing, little movement of the rib cage, muffled cough and reduced vital capacity. Prompt reduction of respiratory excursions and vital capacity may occur following

repeated deep breathing or a rapid series of coughs.

About the hips the iliopsoas group is most frequently involved. This may be detected on flexion of the thigh at the hip and by having the patient repeatedly cross and uncross the knees in the sitting position. The abductors of the thighs at the hips are more frequently involved than the adductors, and the knee flexors more frequently than the extensors. The dorsiflexors and everters of the foot at the ankle as well as the extensors of the toes are more commonly involved than the plantar flexors and the inverters of the feet. For this reason the patient is often able to walk on the toes but is unable to walk on the heels or raise the forefoot off the floor in the standing position with the heel still touching the floor. (See Table 2.)

Diagnostic Measures

The diagnosis of myasthenia gravis should be suspected in patients complaining of muscle weakness and easy fatigability of muscle strength.[7,18] Tests may include having the patient sustain upward gaze to note any fatigue of the levators of the lids or the extraocular muscles. Continuous counting may detect fatigue of speech. Holding the arms extended or over the head may show fatigability of these muscles. Other means of demonstrating increased muscle weakness are repeated crossing and uncrossing of the legs, squatting exercises and repeated compression of a rolled-up and inflated blood pressure cuff or dynamometer with the hand. Fatigability should be searched for in these various muscle groups.

TABLE 2.—*Frequently Involved Muscles of Patients with Myasthenia Gravis**

Muscle or Muscle Groups	*Incidence (Per Cent) in* *Males*	*Females*	*All Patients*
Lid levator	58	59	58
Extrocular muscles	63	47	54
Jaw	31	32	32
Orbicularis oculi	76	66	71
Face	64	62	63
Deglutition	20	26	24
Voice	28	37	33
Tongue	36	31	33
Neck	57	63	61
Shoulder and arm	73	71	72
Hand and finger	70	66	68
Leg	74	76	75
General	10	12	11

*Findings from 177 patients with myasthenia gravis (102 females and 75 males) seen by the author in the myasthenia gravis clinic and Division of Neurology at UCLA School of Medicine, Los Angeles.

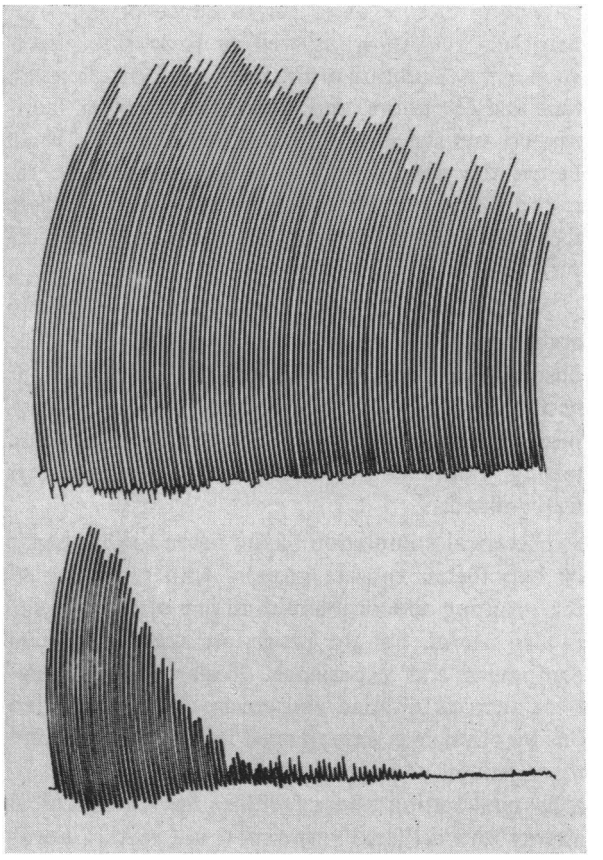

Figure 1.—Bulb ergograph tracings of the hand grips in normal person (above) and myasthenic patient (below) showing pronounced reduction in effective strength in the patient after approximately 30 squeezes in 30 seconds.

In the bulb ergograph test of the hand grip, the patient squeezes a rubber bulb similar to that on a sphygmomanometer at one-second intervals signaled by a bell. The bulb is attached to an ink-writing kymograph (Figure 1).

Another feature of myasthenia gravis is generally improved strength on administration of anticholinesterase drugs. The response to anticholinesterase therapy should be preceded by baseline observations of strength in several muscle groups as well as observations after a protective placebo injection of atropine to evaluate the psychologic aspects and suggestibility of the patient. The atropine also serves to protect the patient from the sometimes unpleasant or toxic cholinergic side effects of the anticholinesterase medication to follow. After a second period of rest for five to 10 minutes, he is given an injection of 1 to 2 mg of edrophonium (Tensilon®) intravenously and then is tested again.[15] If there is no favorable response to this dosage, a larger dose, 4 to 8 mg, may be given after another five to 10 minutes of rest. The

patient is then retested for evidence of improvement or weakening as well as toxic side effects such as fasciculation of the muscles about the eyes, face and elsewhere, and increased salivation, lacrimation and sweating. Muscles detected to be weak before the administration of drugs should be retested systematically following each dose to note the presence or absence of any significant improvement or increased weakness.

Measurement of vital capacity as well as bulb ergograph tests may be used along with other observations for confirmatory help. Intramuscular neostigmine U.S.P. (Prostigmin®) or pyridostigmine (Mestinon®) may also be used for diagnostic testing, but results are slower and at times less well defined.

Electrical stimulation of the nerve to the thenar or hypothenar muscle groups, with recording of the resulting action potential in one of these areas, is also useful, but the procedure requires special equipment and experience. Tests with provocatives such as quinine and curare are best carried out by physicians experienced in the diagnosis and management of patients with myasthenia gravis in a hospital setting where facilities for a mechanical airway and artificial respiration are readily available.

TABLE 3.—*Other Disorders Entering the Differential Diagnosis of Myasthenia Gravis*

Adynamia episodica hereditaria
Amyotrophic lateral sclerosis (Progressive spinal muscular atrophy and progressive bulbar palsy)
Botulism
Catalepsy
Chlorothiazide or hydrochlorothiazide electrolyte depletion
Cholinergic crisis
Dermatomyositis
Familial periodic paralysis
Hyperparathyroidism
Hyperthyroidism
Multiple sclerosis
Myasthenic syndrome associated with anaplastic malignant disease
Myasthenic component in other myopathic states
Myotonia atrophica
Narcolepsy
Phosphorylase deficiency myopathy (McArdle's syndrome)
Polymyositis
Polyneuropathy
Primary aldosteronism
Progressive external ophthalmoplegia
Progressive muscular dystrophy
Psychogenic asthenic reaction

Routine x-ray films of the chest should include posteroanterior and lateral views. Lateral laminograms of the anterosuperior mediastinum may also be helpful in detecting the presence or absence of thymic hyperplasia or thymoma, but distinguishing between thymic hyperplasia and thymoma on radiographic findings alone is difficult or impossible.

There are at present no specific laboratory tests for myasthenia gravis. A partial list of other disorders entering into the differential diagnosis of myasthenia gravis is given in Table 3.

Therapy

Treatment may be started with oral administration of Prostigmin® 7.5 to 15 mg or Mestinon 30 to 60 mg two or three times daily, preferably one-half to three-quarters of an hour before meals.[11,19] The drugs may be taken with milk and crackers or bread, but should not be taken with coffee, fruit or tomato juice since they may enhance the parasympathomimetic side effects on the bowel and bladder. Dosage should be increased cautiously and only if followed by significant objective improvement in symptoms. Data on common anticholinesterase drugs are summarized in Table 4. Seldom does use of any of them bring about more than 80 per cent restoration of the normal muscle strength and performance. Even with optimal therapy a few patients do not respond significantly to anticholinesterase medication. It must be kept in mind that there is no evidence for a lack of anticholinesterase in the patient with myasthenia gravis and that these drugs are not normally present or lacking in the patient with myasthenia gravis. They are mainly pharmacological crutches used to facilitate what remains of neuromuscular transmission which is already defective in the myasthenic patient. An excess of anticholinesterase drug can produce increased weakness beyond that already caused by myasthenia gravis. Also a host of unpleasant, and at times serious, side reactions are produced.

Crisis

Myasthenia gravis may be aggravated by infections elsewhere in the body, particularly those involving the respiratory tract. It may also be aggravated by emotional stress and menses. The myasthenic process may increase to such proportions that the patient is said to have a myasthenic crisis.[5,8,14] In this circumstance the patient is

TABLE 4.—*Common Anticholinesterase Drugs Used in Diagnosis and Management of Myasthenia Gravis*

Drug	*Form*	*Adult Single Dose and Route*	*Usual Effective Duration and Range*
Tensilon® (Edrophonium chloride)	10 mg per ml	2-10 mg IV	10 minutes (2 min.-2 hours)
Prostigmin® (Neostigmin methyl sulfate)	0.25, 0.5 and 1.0 mg per ml	1 mg IM	2 hours (2-4)
Prostigmin® (Neostigmin bromide)	15 mg tablet	15 mg oral	3 hours (2-5 hours)
Mestinon® (Pyridostigmin bromide)	60 mg tablet	60 mg oral	4 hours (3-7 hours)
Mestinon Timespan® (Pyridostigmin bromide)	180 mg tablet (slow release)	180 mg oral	8 hours (6-12 hours)
Mestinon syrup® (Pyridostigmin bromide)	60 mg per 5 ml syrup	60 mg per 5 ml (1 tsp oral)	4 hours (3-7 hours)
Mytelase® (Ambenomium chloride)	10 mg and 25 mg tablets	10-25 mg oral	8 hours (6-10)

IV=Intravenous; IM=Intramuscular.

unable to maintain a patent airway or adequate respiratory exchange. In some instances this may result from inadequate anticholinesterase treatment; if so, an increase in the anticholinesterase dosage may help. Other patients may be unresponsive or insensitive to increased doses of anticholinesterase. In still others, weakness—called "cholinergic crisis" — may be provoked by an excess amount of anticholinesterase. The symptoms and signs of myasthenic and cholinergic crisis are listed in Table 5.

At times Tensilon may be used successfully to determine the need for more longer-acting anticholinesterase.[15] If the patient responds favorably to Tensilon, he may benefit from increased dosage of longer-acting anticholinesterase medication. However, in some patients there may be a positive response to Tensilon but no improvement, even deterioration of strength, following additional dosage of longer-acting anticholinesterase. Under these circumstances bedrest, tracheostomy, controlled or assisted mechanical respiration and withdrawal of anticholinesterase may be the treatment of choice.[5,8,14] This may be best handled in an intensive care unit facility for patients with chronic respiratory insufficiency or in a center dealing frequently with myasthenia gravis patients. At times it is difficult if not impossible to determine with certainty what kind of crisis is occurring —whether myasthenic, cholinergic, a combination of these or the so-called "insensitive state." Under these circumstances prompt control of the airway

TABLE 5.—*Symptoms and Signs of Myasthenic and Cholinergic Crisis*

Myasthenic Crisis	*Cholinergic Crisis*	
	Muscarinic Symptoms and Signs:	Nicotinic Symptoms and Signs:
Ocular ptosis	Sweating	Muscle fasciculations
Dysarthria or anarthria	Lacrimation	"Thick tongue"
Dysphagia or aphagia	Salivation	Dysarthric speech
Dyspnea or apnea	Anorexia	Dysphagia
Facial weakness	Abdominal cramping	Trismus
Masticatory weakness	Diarrhea	Muscle cramps and spasms
Difficulty handling secretions	Nausea	General weakness
General weakness	Vomiting	
	Urinary frequency	CNS Symptoms and Signs:
	Incontinence of bowel and bladder	Restlessness
	Miosis	Anxiety
	Blurred vision	Giddiness
	Bronchorrhea	Vertigo
	Dyspnea and wheezing	Headache
	Substernal pressure	Confusion and stupor
	Bronchospasm	Coma
	Pulmonary edema	Convulsions

and respirations should be obtained along with adequate tracheobronchial toilet and control of infection if present. After several days the patient's vital capacity may again improve along with strength elsewhere. Ultimately he may be able to manage for several days or weeks without anticholinesterase medication.

When administration of anticholinesterase is resumed, it should be started in low dosage and increased slowly.

Atropine to counteract parasympathomimetic or muscarinic side effects is fraught with hazards and it should be used sparingly if at all.[18] As this tends to mask the early signs of cholinergic intoxication, the patient may pass directly into the nicotinic or paralytic phase of cholinergic intoxication without other warnings. Also oropharyngeal and bronchopulmonary secretions are suppressed and they become tenacious and exceedingly difficult to remove. The patient seldom gains much improvement in voluntary muscular strength from additional anticholinesterase dosage once symptoms and signs of parasympathomimetic or muscarinic toxicity are present or suppressed with atropine or a similar parasympathetic blocking agent.

It is important for both the patient and his physician to understand that if one dosage level of anticholinesterase produces favorable effects, twice the dosage will not necessarily double the improvement, and it may increase weakness. Common side effects from anticholinesterase medication include increased sweating, salivation, abdominal cramps, diarrhea and urinary urgency and frequency.

Indications for Thymectomy

Thymectomy appears helpful in younger patients who have had myasthenia gravis less than five to seven years and who do not have a thymoma.[1,6,9,16] However, thymectomy is also indicated in patients suspected of having thymoma, since these tumors may increase in size and thus embarrass other intrathoracic structures. At times they also undergo malignant change. Patients with thymoma do less well with thymectomy than those with thymic hyperplasia. There is no evidence, however, that thymectomy in patients with thymoma unfavorably affects the course of myasthenia. Thymectomy should not be undertaken as an emergency procedure in a patient who is going rapidly down hill with myasthenia gravis or in one who is pregnant or who has active pulmonary inflammatory process.

While myasthenia gravis is a disorder often marked by remissions and exacerbations, a certain number of patients also achieve complete remission and freedom from symptoms, and no longer need anticholinesterase medication. With appropriate patient education, physician understanding, drug therapy and selective thymectomy, the majority of patients with myasthenia gravis may get along well.

Generic and Trade Names of Drugs

Endrophonium—*Tensilon.*®
Neostigmine U.S.P.—*Prostigmin.*®
Pyridostigmine—*Mestinon.*®

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